

The Id3/E47 axis mediates cell cycle control in human pancreatic ducts and adenocarcinoma.

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Public Summary:

Pancreatic ductal adenocarcinoma (PDA) has a five-year survival rate of less than 5%, and therapeutic advances have been hampered by gaps in our understanding of cell cycle control in the adult pancreas. Previously, we reported that basic Helix-Loop-Helix (bHLH) transcription factors regulate cell fate specification in the pancreas. In the present study we found that a repressor of bHLH activity, Id3, was profoundly upregulated in ductal cells in murine models of pancreatitis and pancreatic intraepithelial neoplasia (PanIN). Id3 was also pervasively expressed in neoplastic lesions in human PDA in situ. We hypothesized that an imbalance in bHLH versus Id activity controlled cell growth in PDA. Consistent with this model, cell cycle progression in PDA cells was impeded by siRNA-mediated depletion of Id3 or overexpression of the bHLH protein E47. The precursors of human PDA are normally quiescent duct cells which do not proliferate in response to high serum or growth factors. The finding that Id3 was expressed in pancreatitis, as well as PDA, suggested that Id3 might induce cell cycle entry in ducts. To test this hypothesis, primary human pancreatic duct cells were transduced with an adenovirus expressing Id3. Remarkably, Id3 expression alone was sufficient to trigger efficient cell cycle entry, as manifested by expression of the proliferation markers Ki67, phospho-cyclin E, and phospho-HH3. Collectively, the data establish dysregulation of the bHLH/Id axis as an early and sustained feature of ductal pathogenesis and mark this axis as a potential therapeutic target for intervention in pancreatitis and PDA.

Scientific Abstract:

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